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Original Contributions

RELATIONSHIP BETWEEN CENTRAL AND PERIPHERAL VENOUS OXYGEN SATURATION AND LACTATE LEVELS: A PROSPECTIVE STUDY

Nikhil Goyal, MD,*† Andrew R. Taylor, MA,‡ and Emanuel P. Rivers, MD*§

*Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan, †Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan, ‡Department of Public Health Science, Division of Biostatistics, Henry Ford Health System, Detroit, Michigan, and §Department of Surgery, Henry Ford Health System, Detroit, Michigan

Reprint Address: Nikhil Goyal, MD, Department of Emergency Medicine, Henry Ford Health System, 2799 W. Grand Blvd., CFP-259, Detroit, MI 48202

☐ **Abstract—Background: Optimization of tissue oxygen delivery to meet consumption demands is important in the resuscitation of critically ill patients. Central venous oxygen saturation ($ScvO_2$) and lactate levels are often used to guide resuscitation; however, invasive monitoring is required for the former. Clinicians searching for less invasive alternatives may consider using peripheral venous oxygen saturation ($SpvO_2$) and lactate levels as a substitute. Objectives: To determine the relationship between $SpvO_2$ and $ScvO_2$ and peripheral and central lactate levels. Methods: All patients with a central venous catheter in an academic emergency department and intensive care unit were eligible for the study. Blood was obtained simultaneously from a central and peripheral vein and measured for oxygen saturation and lactate levels. Results were analyzed using intraclass correlation coefficient (ICC), Bland-Altman plots, and receiver operating characteristic curves. Results: Seventy-nine paired blood samples were analyzed. $SpvO_2$ and $ScvO_2$ have moderate agreement: ICC = 0.53 (95% confidence interval [CI] 0.35–0.67). A Bland-Altman plot revealed substantial bias (−4.47; limits of agreement −38.6, 29.6). $SpvO_2 \geq 85\%$ was 90% specific for $ScvO_2 \geq 70\%$, and $SpvO_2$ of $\leq 55\%$ had a 94% sensitivity for $ScvO_2 < 70\%$. Central and peripheral venous lactate levels showed almost perfect agreement: ICC = 0.92 (95% CI 0.87–0.95), bias of 0.46 (limits of agreement −1.78–2.70). Conclusion: $SpvO_2$ and $ScvO_2$ have moderate agreement. There was excellent agreement between peripheral and central lactate levels, making them interchangeable. The clinical implications of these substitutions in real-time patient management require further study.** © 2016 Elsevier Inc. All rights reserved.

☐ **Keywords—central venous; peripheral venous; oximetry; veins; resuscitation; lactic acid; shock**

INTRODUCTION

Early hemodynamic optimization of shock consists of the optimization of cardiac preload (reflected in central venous pressure [CVP] or surrogate), afterload (mean arterial pressure), and contractility (cardiac output/heart rate) (1). The critical oxygen delivery threshold (when systemic oxygen delivery [DO_2] meets consumptive demands) is then confirmed by normalization of central venous oxygen saturation ($ScvO_2$) or mixed venous oxygen saturation (SvO_2), and lactate levels (2). Maneuvers to achieve this balance include optimizing arterial oxygen content (by addressing oxygen saturation and hemoglobin), improving cardiac output (inotropic agents), and decreasing systemic oxygen consumption (via mechanical ventilation and muscle relaxation). The Surviving Sepsis Campaign recommends, as one of the options, that a patient with sepsis-induced tissue hypoperfusion

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have protocolized resuscitation with a goal of $ScvO_2$ of 70% or higher in the first 6 hours of resuscitation (grade 1C) and targeting resuscitation to normalize lactate (grade 2C) (3). Detection of hyperlactatemia is a key component of the diagnostic criteria for sepsis, severe sepsis, and septic shock (4).

The administration of vasopressors, measurement of CVP, and intermittent or continuous $ScvO_2$ measurement requires placement of a central venous catheter (CVC). This procedure carries some degree of risk, requires expertise, and is thought to be resource intensive (5). Recently there has been renewed interest in exploring alternative resuscitation methods, potentially decreasing the need for invasive monitoring (6–8). Physicians working in the Emergency Department (ED) often encounter critically ill patients with unclear etiologies of shock and with varying degrees of prior resuscitation. In addition, they may not have immediate access to advanced or invasive hemodynamic monitoring. The peripheral venous oxygen saturation ($SpvO_2$) is a single measurement of the oxygen saturation of peripheral venous blood and may be easily performed in inpatient and outpatient settings; it involves minimal risk. Based on this rationale, ED physicians may be inclined to utilize $SpvO_2$ or peripheral lactate to manage their patients. There are few data regarding the agreement between $ScvO_2$ and $SpvO_2$ (9–11). Similarly, there is a lack of data on agreement between central and peripheral venous lactate levels (12–16).

This study was conducted to compare $SpvO_2$ and $ScvO_2$ and to compare peripheral and central lactate levels in an unselected population of patients. Our secondary objective was to determine if a high $SpvO_2$ could be used to exclude a low $ScvO_2$.

MATERIALS AND METHODS

Study Design

This was a prospective observational study conducted from August 2004 to August 2006. All adult patients at Henry Ford Hospital with a CVC were eligible for the study. The decision to place the CVC was made by the treating physician with no input from the study investigators; patients were enrolled in the study only if a CVC had already been placed. We excluded any patient who needed a CVC placed due to an inability to obtain adequate peripheral intravenous access; it was felt that attempts to obtain a peripheral venous sample in such patients could involve significant discomfort to the patient. Patients were identified in the ED and intensive care unit in order to evaluate patients with varying degrees of resuscitation.

Approximately 0.5 mL of blood was collected from the CVC after an adequate waste draw. Immediately thereafter, an additional 0.5 mL of blood was obtained from a preexisting peripheral intravenous site (after an adequate waste draw) or via peripheral stick. The site for peripheral blood sampling was determined by the treating nurse with the intent to minimize patient discomfort. Any fluid or medications infusing into the same limb were discontinued for the duration of the blood sampling. Oxygen saturation and lactate levels were measured from both samples after immediate transport to the blood gas laboratory. CVC site and site of peripheral blood draw were recorded. If a tourniquet was used to draw the peripheral sample, tourniquet time was also recorded as an estimate by the person who drew the blood. Blood gas analysis results from the CVC sample were available to the treating physician to use in patient management; the peripheral venous blood gas analysis was not part of the medical record.

All blood gas and lactate measurements were done on a Ciba ABL 800® blood gas analyzer. Prior approval was obtained from the institutional review board; the requirement for informed consent was waived. In many cases the blood samples were collected when blood cultures were being drawn from central and peripheral sites, eliminating the need for additional blood draws.

Statistical Analysis

A convenience sample was chosen for this study based on investigator availability. We did not prespecify any subgroup analyses or attempt to stratify patients by presence or absence of shock. Age, tourniquet time, and serum lactate data were summarized using means and standard deviations. For these calculations, any samples with missing data were excluded from the respective analyses. Any tourniquet times recorded as "less than 5 minutes" were interpreted as 5 min. The intraclass correlation coefficient (ICC) was used to calculate the agreement between $ScvO_2$ and $SpvO_2$. The ICC was also used to measure the agreement between lactate measured from central and peripheral blood. The agreement between the $ScvO_2$ and $SpvO_2$ and lactate levels were assessed using Bland-Altman plots. The mean bias and 95% limits of agreement were calculated.

For the secondary objective, we used the receiver operating characteristic curve to evaluate various thresholds of $SpvO_2$ to predict the gold standard of $ScvO_2 \geq 70\%$. The cutoff value was determined to have high specificity.

For all measures, distributional assumptions were checked and transformations were made when appropriate. Specifically, both $SpvO_2$ and $ScvO_2$ showed significant left skew and were square transformed prior to performing the ICC analysis. Similarly, lactate levels at both locations showed significant right skew, and were log transformed prior to performing the ICC analysis.

RESULTS

Eighty-eight patients were enrolled in the study. Data from 9 were not included in the analysis due to missing elements (i.e., either $SpvO_2$ or $ScvO_2$ were not measured); data from the remaining 79 paired blood samples were analyzed. The mean age was 67 ± 15.5 years, and 38% were female. Most patients (70, 89%) were enrolled in the ED, whereas the remaining were enrolled in the intensive care unit. For our primary analysis (the agreement between $SpvO_2$ and $ScvO_2$), the ICC was 0.53 (95% confidence interval [CI] 0.35–0.67), which relates to moderate agreement (17).

The Bland-Altman plot for venous oxygen saturation is shown in Figure 1. The x-axis represents the average of two measurements ($SpvO_2$ and $ScvO_2$), with the oxygen saturation across the range between 34 and 96. The y-axis represents the difference in two oxygen saturation measurement methods. The bias is −4.47, indicating the measurement from peripheral venous blood is 4.47% (absolute) lower than the one from central venous blood. The standard deviation of the differences between the two methods is 17.4 (95% limits of agreement: −38.6, 29.6). Based on this figure, there are two measurements exceeding the upper or lower limit of agreement. The plot suggests the differences between the two methods are greater when oxygen saturation is > 80% and smaller when it is < 60%. The Shapiro-Wilk normality test showed that the difference is approximately normal ($p = 0.064$). The percentage error is 47% (95% CI 13.3–81.5).

Serum lactate levels were not measured for four peripheral samples and six central samples. The peripheral and central venous lactate levels showed almost perfect agreement (ICC = 0.92, 95% CI 0.87–0.95). Figure 2 shows the Bland-Altman plot for lactate levels. Bias was computed as the lactate level in peripheral blood minus the lactate level in central blood; on average, lactate levels were 0.46 mmol/L higher in peripheral blood than central blood (limits of agreement −1.78, 2.70). According to the plot, there are three measurements outside the limits of agreement. The percentage error is 57.9% (95% CI 55.7–61.2).

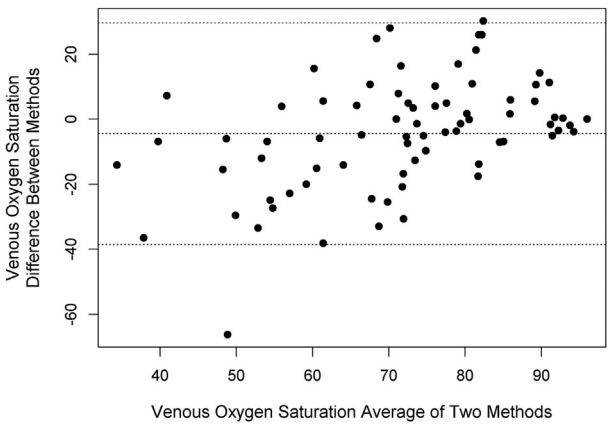

Figure 1. Bland-Altman plot for venous oxygen saturation.

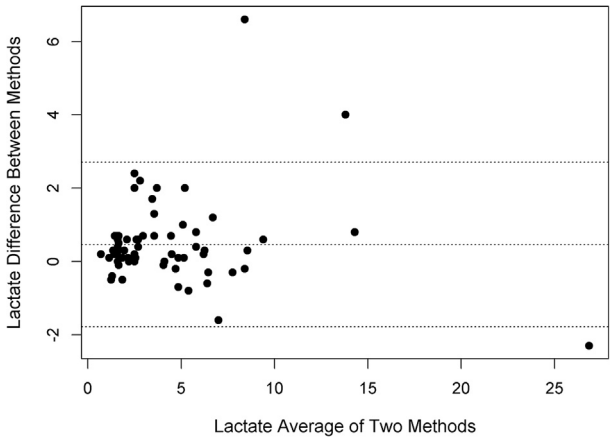

Figure 2. Bland-Altman plot for lactate.

For the secondary analysis, we calculated the test characteristics of $SpvO_2$ at various thresholds when compared with the gold standard of $ScvO_2 \geq 70\%$. The sensitivities (true positive rates) and specificities (true negative rates) using thresholds of $SpvO_2$ ranging from 55% to 90% are listed in Table 1. The receiver operating characteristic curve is displayed in Figure 3, and the area under the receiver operating characteristic curve is 0.77 (95% CI 0.654–0.892). The results demonstrate that we have 90% specificity of $ScvO_2 \geq 70\%$ (95% CI 0.735–0.979) when the threshold of $SpvO_2$ is set at 85%.

Tourniquet time was not recorded for 11 peripheral blood samples and "less than 5 minutes" was recorded for 5. The average tourniquet time was 1.61 ± 1.63 min (97 ± 97.8 s). These data are summarized in Table 2.

DISCUSSION

Shock, irrespective of etiology, begins with a host–pathogen interaction that elicits an intricate interplay between

Table 1. Sensitivity and Specificity of Using $SpvO_2$ at Various Thresholds for Predicting $ScvO_2 \geq 70\%$

$SpvO_2$ Threshold (%)	Sensitivity*	Specificity*
55	0.939 (0.831–0.987)	0.533 (0.343–0.717)
60	0.857 (0.728–0.941)	0.600 (0.406–0.773)
65	0.816 (0.680–0.912)	0.667 (0.472–0.827)
70	0.755 (0.611–0.867)	0.733 (0.541–0.877)
75	0.612 (0.462–0.748)	0.767 (0.577–0.901)
80	0.510 (0.363–0.656)	0.833 (0.653–0.944)
85	0.367 (0.234–0.517)	0.900 (0.735–0.979)
90	0.265 (0.149–0.411)	0.900 (0.735–0.979)

* Numbers in parentheses reflect 95% confidence intervals.

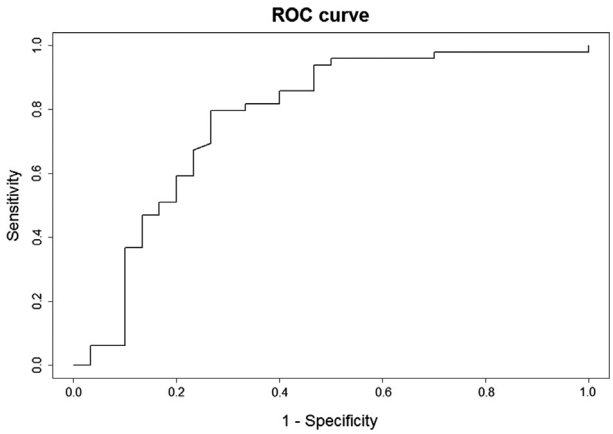

Figure 3. Receiver operating characteristic (ROC) curve for detection of central venous oxygen saturation ≥ 70%.

proinflammatory, antiinflammatory, and apoptotic mediators (18). Hypovolemia, myocardial depression, increased metabolic demands, and vasoregulatory perfusion abnormalities eventually result in organ dysfunction from circulatory insufficiency. The net effect of these is an imbalance between systemic oxygen supply and demand, leading to global tissue hypoxia. This pathogenic event significantly contributes to the morbidity and mortality of shock (19,20).

A critical decrease in DO_2 is followed by an increase in the systemic oxygen extraction ratio (OER) and a decrease in $ScvO_2$ or SvO_2 (Figure 4) (21–23). This increase in OER is a compensatory mechanism to match systemic oxygen demands. When the limit of this compensatory mechanism (OER > 50% to 60%) is reached, anaerobic metabolism ensues, leading to lactate production (2). In this critical delivery-dependent or hypodynamic phase, lactate concentrations are inversely related to DO_2 and SvO_2 (24). This phase can occur with normal vital signs and is referred to as "occult shock," where the patient outwardly appears less ill. As a result, organ dysfunction and sudden cardiopulmonary collapse are complications associated with this phase if it is unrecognized or left untreated (19,21,25).

The basic pathogenesis of shock (regardless of etiology) is this imbalance between DO_2 and tissue oxygen requirements (reflected in SvO_2 measurements) that leads to an inability to maintain cellular aerobic respiration (reflected in lactate concentration) (26). For instance, pump failure leads to cardiogenic shock due to insufficient cardiac output affecting DO_2 (Figure 4), or decreased hemoglobin leads to low DO_2 in hemorrhagic shock. Septic shock has multiple metabolic derangements, including increased oxygen requirements (VO_2), decreased cardiac output, and cellular inability to utilize delivered oxygen (27,28).

After adequate resuscitation, a hyperdynamic phase follows the hypodynamic phase (29). Compensated sepsis is characterized by an elevated SvO_2 and normal lactate; an elevated lactate and elevated SvO_2 denote pathologic delivery dependence or delivery independence and are associated with increased mortality (30). The failure to increase OER, and thus increase VO_2, may be secondary to impairment of microvascular oxygen perfusion or mitochondrial dysfunction.

An $ScvO_2$ of < 70% within the first 6 h is associated with significantly increased mortality, is one of the most important bundle elements, is predictive of outcome, and is superior to physical examination in detecting low cardiac index (30–36). In the presence of a low $ScvO_2$, therapeutic maneuvers to increase DO_2 or decrease VO_2 are required to normalize this value. Thus, $ScvO_2$ becomes a trigger for increasing inspired oxygen concentration (targeting arterial hypoxia), red blood cell transfusion (decreased arterial oxygen content), inotrope therapy (myocardial suppression), and mechanical ventilation (increased oxygen demand) (1,37–40). $ScvO_2$ has also been shown to be predictive

Table 2. Summary Results

	Central Venous Blood	Peripheral Venous Blood	ICC*
Venous O_2 saturation (mean, SD)	73.5 ± 13.3%	69.4 ± 20.6%	0.53 (0.35–0.67)
Veins sampled (n)	Right IJ: 17 Right subclavian: 37 Left subclavian: 8 Right femoral: 4 Left femoral: 1 Not recorded: 12	Right AC: 11 Left AC: 8 Right forearm: 6 Left forearm: 14 Right wrist/hand: 16 Left wrist/hand: 8 Other: 6 Not recorded: 10	
Tourniquet time (median, range)		1 min (0–5)	
Serum lactate (mean, SD)	4.0 ± 3.9 mmol/L	4.3 ± 3.8 mmol/L	0.92 (0.87–0.95)

ICC = intraclass correlation coefficient; SD = standard deviation; IJ = internal jugular; AC = antecubital.
* 95% confidence interval in parentheses.

$CaO_2 = (1.34 \times Hb \times SaO_2) + (0.0031 \times PaO_2)$
$CvO_2 = (1.34 \times Hb \times SvO_2) + (0.0031 \times PvO_2)$
$DO_2 = Q \times CaO_2$
$VO_2 = Q \times (CaO_2 - CvO_2)$
Oxygen Extraction Ratio = $\frac{CaO2 - CvO2}{CaO2}$

Primary determinants of Q: Heart rate, cardiac preload, afterload, contractility

CaO_2 = Arterial oxygen content; Hb = Hemoglobin; SaO_2 = Arterial oxygen saturation; PaO_2 = Partial pressure of oxygen in arterial blood; CvO_2 = Mixed venous oxygen content; SvO_2 = Mixed venous oxygen saturation; PvO_2 = Partial pressure of oxygen in mixed venous blood; DO_2 = Oxygen delivery; Q = Cardiac output; VO_2 = Oxygen consumption

Figure 4. Determinants of tissue oxygenation.

of acute cardiopulmonary decompensation, which is an important attribute in decreasing mortality with early goal-directed therapy (EGDT) (41). Both lactate clearance and SvO_2 have been found to be useful guides for monitoring resuscitation (42,43). They are distinct yet physiologically related; SvO_2 indicates a mismatch between DO_2 and VO_2, whereas lactate reflects cellular anaerobic respiration resulting from the mismatch. Addressing SvO_2 along with lactate may provide the best understanding of oxygen delivery and cellular metabolism (26).

Multiple studies have compared $ScvO_2$ with SvO_2 and show that there is an absolute difference (5%) between the two sites (44,45). Although there is a difference, the clinical utility of both sites is comparable and validated by outcome studies (45). Femoral venous oxygen saturation is not a reliable substitute for $ScvO_2$ (46,47). The relationship between $SpvO_2$ and $ScvO_2$ is less clear, as there are concerns that oxygen extraction from regional tissues may not accurately reflect global tissue perfusion (48). To our knowledge, this is the first study that attempts to accurately identify the relationship between $SpvO_2$ and $ScvO_2$ in a population most likely to benefit from the results (21). Our results describe a moderate agreement between $SpvO_2$ and $ScvO_2$. Previous investigations have described good *correlation* between the two, but there is a lack of analyses on their *agreement* and the clinical utility of $SpvO_2$ measurement (9–11). Correlation implies that two values move in the same direction; high correlation does not mean that the diagnostic measurements agree (49). Our analysis shows that the agreement between $ScvO_2$ and $SpvO_2$ is moderate, and that one cannot be used as a reliable numerical substitute for the other during active management of a patient.

In the presence of shock, venous oxygen saturation can vary in different vascular territories, such as the saturation in the superior vena cava increases compared with a decrease in the inferior vena cava. Skeletal muscle blood flow diminishes in shock as blood is redistributed to the central circulation. The early decrease in blood flow leads to an increase in extraction. However, as the shock state progresses, shunting may occur and there may be a subsequent increase in peripheral venous saturation. The $SpvO_2$ represents a regional DO_2/VO_2 mismatch as opposed to the more global picture presented by the $ScvO_2$ and SvO_2. All peripheral venous blood sampling in this study was done from the upper extremities and therefore does not incorporate venous return from the splanchnic circulation. At least 79% of the central venous sampling was done from the superior vena cava territory (Table 2). We further did not account for exogenous vasopressor therapy, which may shunt blood from the skin to the central circulation.

Based on our data, if a patient has an $SpvO_2 \geq 85\%$, one can be reasonably certain that the $ScvO_2$ is normal (i.e., above the resuscitation goal of 70%). Similarly, an $SpvO_2$ of $\leq 55\%$ indicates that the $ScvO_2$ is likely below the resuscitation goal. An $SpvO_2 < 55\%$ or $> 85\%$ is not unusual; 19 patients (24%) had $SpvO_2 \leq 55\%$ and 21 patients (27%) had $SpvO_2 \geq 85\%$. It is important to recognize that $ScvO_2$ assessment is just one of the recommended resuscitation goals; preload and afterload optimization is also key. If this hypothesis proves true, it could lead to improved compliance with the resuscitation bundle. However, this would still necessitate a surrogate measure of preload assessment.

Recent studies have described management of septic shock patients with EGDT components of early identification, antibiotics, and aggressive fluid resuscitation, without mandatory CVP or $ScvO_2$ goals (6–8). This has led some to question the current utility of invasive central venous monitoring. The results of these studies continue to be debated as the majority of patients in the non-EGDT arms of these trials (57% of standard therapy and 58% of usual-care patients in ProCESS, 62% of usual care patients in ARISE, and 51% of usual resuscitation patients in ProMISe) received a CVC. Subsequent measurement of $ScvO_2$ carries negligible risk to such patients. Although it may be tempting to avoid CVC placement in septic shock patients and potentially use $SpvO_2$ to guide

resuscitation, these trials and our study cannot support this practice.

The high serum lactate concentration for the patients in our study indicates that our population was representative of those in whom an emergency physician would consider aggressive resuscitation. Emergency physicians often encounter patients in undifferentiated shock, and these are the patients most likely to benefit from a definitive determination of preload, afterload, and contractility. Upon presentation to the ED, the etiology and phase of shock and the degree of resuscitation is often unclear. Our study enrolled patients in various phases of resuscitation, to try to establish a relationship between $ScvO_2$ and $SpvO_2$ in a variety of hemodynamic states; however, the attempt was to resuscitate as early as possible. In EDs that have limited capability for CVC placement or continuous $ScvO_2$ monitoring, measurement of $SpvO_2$ may help determine whether early, aggressive management should be reconsidered.

Previous studies have described strong correlation between peripheral and central venous lactate concentration and agreement between arterial and venous lactate (12–14,50–53). Our analysis reveals excellent agreement between central and peripheral venous lactate, with peripheral lactate being slightly higher than central lactate. These data may be useful when trying to assess the rate of decline of lactate concentration between the first blood draw (typically peripheral venous) and subsequent measurements of central venous or arterial lactate. Approximately 95% of the time, the difference between peripheral and central lactate should lie between −1.78 and +2.70; this would indicate that a peripheral lactate level of 6.7 mmol/L would almost certainly indicate a central lactate of ≥ 4 mmol/L and may serve as a prompt to institute further therapy.

Limitations

Tourniquet application for blood draws may alter venous oxygen saturation and lactate concentration of peripheral blood, adversely affecting the described analysis. Tourniquet times in this study were low and were estimated by the provider who obtained the peripheral sample. We excluded patients who did not have adequate peripheral veins, and various sites for peripheral venous sampling were used to minimize patient discomfort. There was no systematic sampling or sample size determination in the study and patients were enrolled as a convenience sample based on investigator availability; this may potentially introduce selection bias. These factors limit the generalizability of the study, specifically to patients who have prolonged tourniquet times or difficult peripheral venous access. There may potentially be stronger agreement between $ScvO_2$ and $SpvO_2$ if specific central and peripheral veins were consistently utilized.

We did not calculate disease severity scores or collect data on patient diagnoses, concurrent therapy, presence or absence of shock, or type of shock. This study reflects patients with and without shock; our intent was to determine the agreement between the $SpvO_2$ and $ScvO_2$ and to determine the need for further study in subsets of patients with specific disease states or vasopressor therapy. Inability to maintain aerobic cellular respiration is the hallmark of shock, regardless of etiology; measurement of lactate and venous oxygen saturation are both important in the care of patients suspected to be in shock (26,54). It is possible that there is a stronger agreement between $SpvO_2$ and $ScvO_2$ in certain types of shock or during particular phases of resuscitation. It is also possible that change in $SpvO_2$ and $ScvO_2$ levels over time may provide useful information. Our study was not designed to address these questions and it is possible that our results may not be applicable to specific subgroups of patients.

Numerical similarity does not equate with similar clinical utility. The one-dimensional substitution of a variable in a protocol with multiple interventions requires unique validation. Although central venous access is more invasive, it has other benefits including the provision of a route for vasopressor therapy, CVP measurement, and intermittent or continuous $ScvO_2$ measurement. $SpvO_2$ measurement does not provide any insight into preload assessment, the critical first step in shock resuscitation protocols. Even if a subsequent study were to demonstrate perfect agreement between $ScvO_2$ and $SpvO_2$, practical benefits of those data are unclear unless validated alternate methods for preload assessment are also implemented.

CONCLUSIONS

$SpvO_2$ and $ScvO_2$ have moderate agreement and one cannot be used as a reliable numerical substitute for the other during resuscitation. There is excellent agreement between peripheral and central lactate levels. The clinical implications of these substitutions in real-time patient management must be validated in further study.

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ARTICLE SUMMARY

1. Why is this topic important?

Early, aggressive, and goal-directed resuscitation of patients in shock can significantly improve mortality. Central venous oxygen saturation ($ScvO_2$) and lactate levels are often used to guide resuscitation, yet their measurement involves additional risk to the patient and may be resource intensive; clinicians often search for a less invasive alternative to help manage their patients, and peripheral venous blood may be used instead.

2. What does this study attempt to show?

Peripheral venous oxygen saturation ($SpvO_2$) is not a reliable substitute for $ScvO_2$. Peripheral and central lactate show excellent agreement.

3. What are the key findings?

$SpvO_2$ and $ScvO_2$ have moderate agreement (intraclass correlation coefficient 0.53, 95% confidence interval [CI] 0.35–0.67). $SpvO_2 \geq 85\%$ is 90% specific for $ScvO_2$ above 70%. $SpvO_2$ of $\leq 55\%$ is 94% sensitive for $ScvO_2$ below 70%. There was almost perfect agreement between peripheral and central lactate levels (intraclass correlation coefficient = 0.92, 95% CI 0.87–0.95).

4. How is patient care impacted?

Before they can be used to impact patient care, these substitutions must be validated in further clinical study after integration into goal-directed resuscitation protocols.